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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM11/1221

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ART UNIT	PAPER NUMBER
1646	47

DATE MAILED: 12/21/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 22 September 1998

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 21-23, 25-27, 31, 33-42 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 21-23, 25-27, 31, 33-42 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

* U.S. GPO: 1998-421-632/40206

Transitional After Final Practice

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's second submission after final filed on 22 September 1998 has been entered.

DETAILED ACTION

2. Claims 21-22, 25-26 and 31 have been amended and claims 33-42 have been added in the amendment filed 22 September 1998. Claims 21-23, 25-27, 31, and 33-42 are currently pending and under consideration in the instant application.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

5. Applicant's arguments filed 22 September 1998 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

6. Claims 40-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 40-41 are directed to a method of making mono-Arg-insulin of formula II. However, the method comprises an additional cleavage step which would result in the formation of insulin, and not mono-Arg-insulin, which is a precursor to mature insulin which lacks an arginine on the terminal end of the B-chain (see step (c)). Therefore, the method of claims 40-41 would not result in the formation of mono-Arg-insulin and the method is therefore not enabled.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 21 and newly submitted claims 33-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) as applied to claim 21 in the prior Office action of paper #41.

Claim 21 is directed to a method of making a compound of insulin using an intermediate compound of insulin [B(1-30)-Arg-A(1-31)]. Newly submitted claims 33-36 are directed to the intermediate compound of insulin, DNA encoding said compound, as well as vectors and host cells for the expression of the DNA. These compounds are obvious over the prior art of record as applied to the method claim 21 for the reasons of record and have been addressed in the sense that the intermediate compound, DNA, vectors and hosts were all required for the method of claim 21 (see paragraph spanning pages 6-7 of paper #41).

Applicant argues at page 10 of response that a prima facie case has not been established because the references (1) fail to teach or suggest the starting materials and (2) fail to teach or suggest the simultaneous addition of trypsin and carboxypeptidase as claimed. These arguments were presented in paper #43 and answered in paper #44 (see page 5 of paper #44). (See also page 8, beginning line 3 of paper #41 and page 5, beginning line 2 of paper #32 where this argument has been responded to before.)

The argument that the generic formula of Markussen et al. encompasses a very large number of species was made in paper #43 and answered in paper #44 at page 6, in addition to addressing *Baird.* The argument that Grau describes the cleavage of a different compound with the simultaneous addition of trypsin and carboxypeptidase was made in paper #43 and answered in paper #44 at page 6.

9. Claims 25 and newly submitted claims 37-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO

163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332), further in view of Mai et al for the reasons of record in paper #41 as applied to claim 25.

Claim 25 is directed to a method of making mono-Arg-insulin using an intermediate compound of insulin which is a fusion protein with a particular bridging peptide. Newly submitted claims 37-38 are directed to the fusion protein of insulin and a method of using the fusion protein. These compounds are obvious over the prior art of record as applied to the method claim 25 for the reasons of record and have been addressed in the sense that the fusion protein and methods of use were all required for the method of claim 25 (see page 10 of paper #41).

The argument that "claim 25 is not obvious over the prior art as it has a novel and nonobvious bridging member" was made in paper #43 and answered in paper #44 at page 8, as well as the argument that the rejection is one of "obvious to try".

10. Claims 22 and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332) for the reasons of record in paper #41.

The argument that the Office has not shown the formation of mono-Arg-insulin as an intermediate was presented in paper #43 and answered in paper #44 at page 9.

11. Claims 26-27 and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Markussen et al. (U.S. Pat. No. 4,916,212) or Markussen et al. (EPO 163,529) either in view of Goeddel et al. (EPO 055,945), Mai et al., Grau (U.S. Pat. No. 4,801,684) and Grau (U.S. Pat. No. 4,639,332), for the reasons of record in paper #41.

Applicant argues points that have already been addressed and answered in paper #44, as well as addressed above. Applicant again contends that there are "apparent misperceptions of the Examiner concerning miniproinsulin and mono-Arg-insulin. This assertion is misplaced in that the Examiner made it clear that there was no confusion regarding the two compounds in paper #41 (see paragraph spanning pages 14-15). Applicant asserts that the Examiner states that mono-Arg-insulin is a species of miniproinsulin and is encompassed within the broad genus disclosed by Markussen. This assertion is without a basis in fact. In a review of paper #44 and #41, the Examiner never states that mono-Arg-insulin is a species of miniproinsulin or that mono-Arg-insulin is encompassed by the broad genus of Markussen. Rather, the miniproinsulin of the instant claims is made obvious by the teachings of Markussen and Grau, because it is the miniproinsulin that can be used to make the mono-Arg-insulin that is suggested by Grau as having superior stability. Applicant is correct that Markussen does not disclose a generic formula that would encompass mono-Arg-insulin (see response at page 15), however, Markussen was not cited for this element. Applicant also states that the mono-Arg-insulin of Grau would not fit into the generic formula of Markussen; this is correct because mono-Arg-insulin is not a miniproinsulin, as pointed out by Applicant.

Applicant argues that the Markussen references are directed to methods of producing insulin precursors wherein the A and B chains of insulin are still joined as a single chain. However, the Markussen references are directed to more than just the precursors, in that the Markussen also teaches the production of insulin by in vitro conversion of the precursors. Applicant argues that the method of cleavable of Markussen only used L-threonine esters. This may be true, but Markussen was not relied upon for the element of conversion of miniproinsulin to mono-Arg-insulin. This element is provided by Grau (see paper #41 at page 7). The fact that Markussen uses a different method for the generation of insulin from the precursor alone is not evidence that those skilled in the art would not have expected trypsin to cleave at the C-terminus of a bridging Arg residue in the single chain precursor to generate the two chain insulin as asserted by Applicant at page 15 of the response.

Applicant further argues the Thim et al. reference. However, this argument has been presented before in paper #31 and answered in paper #32.

Applicant asserts that "the Examiner has also failed to suggest using the specifically claimed miniproinsulin (B(1-30)-Arg-A(1-21)) in any method" (see response at page 17). This assertion is without a basis in fact and is supported by the rejections which have been made and detailed in paper #41 and maintained in the instant Office action. Applicant also asserts that the Examiner "has provided no reasons why one would have selected the miniproinsulin as the starting material to produce insulin". This statement is also without a basis in fact in that express motivation for using this particular compound was identified in the grounds of rejection of paper #41 and maintained in the instant Office action.

Applicant's argument regarding Grau ('684) is that Grau is directed to methods of obtaining insulin precursors, and not insulin from mono-Arg-insulin. This is correct, because if Grau taught preparation of insulin from mono-Arg-insulin, the rejection would have been made under 102, anticipation, and not 103, obviousness.

Applicant's point that the method of Grau is different than the instant method because porcine proinsulin is used is noted. However, it still does not teach away from the fact that trypsin and carboxypeptidase B can be simultaneously added together for the cleavage of a protein, which is why Grau ('684) was cited.

Applicant's arguments regarding the kinetics of the trypsin cleavage for mono-Arg-insulin versus porcine insulin are appreciated, but are not persuasive. Grau ('332) specifically teaches that treatment of proinsulin with trypsin alone gives intermediates with an arginine at B31. This insulin-Arg^{B31}-OH derivative is stable to further tryptic degradation. Grau ('332) also teaches that enzymes having both tryptic and carboxypeptidase B activity are required to produce insulin. (See column 1, lines 1-32; column 2, lines 10-12.) Therefore, one of skill in the art would have a reasonable expectation of success in using these two enzymes for the production of insulin since it was accepted in the art that these two enzymes are required to produce insulin, absent evidence to the contrary.

12. Claims 39 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. ('828) either in view of Grau ('684) and Grau ('332).

The references are as described above. The intermediate disclosed by Grau ('332) is the mono-Arg insulin of formula II. It would have been prima facie obvious to one of ordinary skill in the art to prepare the mono-Arg-insulin by expressing a DAN molecule encoding miniproinsulin in either bacteria or yeast as taught by Markussen et al. and cleaving this compound with trypsin as taught by Grau ('332 and '684) to produce mono-Arg-insulin. One would have been motivated to produce a stable intermediate of insulin for further treatment with carboxypeptidase B to produce insulin for treating diabetes. One would further be motivated to make the mono-Arg-insulin because Grau ('332) teaches that mono-Arg-insulin is resistant to further tryptic degradation, and would therefore, be a stable intermediate for the future formation of insulin.

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 3PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 308-0294. Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December 21, 1998

Christine Saoud, Ph.D.
Christine Saoud
Patent Examiner
Art Unit 1646